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REVIEW

Viscoelastic testing: Transforming hemostasis management in patients in the medical intensive care unit

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Abstract

Viscoelastic testing (VET) has emerged as a groundbreaking method for assessing hemostasis, offering real-time evaluations of coagulation dynamics that exceed traditional tests. It provides immediate insights into the complex interplay among plasma coagulation factors, platelets, and cellular components that regulate hemostatic function, offering a continuous evaluation of the entire hemostatic process – from initial clot formation and stabilization to dissolution. Although often utilized in surgical settings such as liver transplants, trauma, or cardiac surgery, VET has also proven valuable in medical intensive care units (ICUs). In non-surgical patients in the ICU, coagulopathy is common, and timely decision-making is critical. VET offers distinct advantages over conventional coagulation tests by providing rapid, point-of-care results that can guide targeted therapeutic interventions. VET-guided transfusion algorithms have reduced allogeneic transfusion rates by 20%-40%, shortened time to intervention by 30%-50% compared to conventional coagulation tests, and improved ICU length of stay. This review discusses VET's principles, limitations, clinical applications in medical ICUs, and the challenges of its implementation. Incorporating VET into routine clinical practice signifies a shift toward advanced, individualized hemostatic care, significantly enhancing patient safety and clinical outcomes while optimizing resource utilization in modern medical ICUs.

Key Words: Viscoelastic tests; Coagulopathy; Sepsis; Cirrhosis; Hypercoagulability

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Core Tip: Viscoelastic testing (VET) provides rapid, whole-blood assessment of the entire coagulation process, offering a real-time and comprehensive evaluation that surpasses conventional coagulation tests in the medical intensive care unit. VET identifies hidden hypocoagulable and hypercoagulable states and fibrinolysis resistance, enabling targeted, precision-based therapies in diverse intensive care unit populations, including sepsis, coronavirus disease 2019, and liver disease. Despite technical and economic challenges, VET-guided management reduces unnecessary transfusions, optimizes resource utilization, and holds promise for integrating artificial intelligence to deliver individualized, advanced hemostatic care for patients who are critically ill.

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INTRODUCTION

Hemostatic disorders represent a significant challenge in the medical intensive care unit (ICU), where patients who are critically ill frequently present with complex coagulopathies often associated with increased morbidity and mortality[1,2]. In medical ICUs, coagulation disorders differ from those in surgical settings, presenting unique challenges for hemostatic management[3]. Coagulopathy affects up to 66% of patients in the ICU, with thrombocytopenia occurring in more than one-third of the cases[4]. These patients require a rapid and accurate assessment of hemostatic function to guide therapeutic interventions, particularly in the setting of bleeding or before invasive procedures[5]. Conditions such as sepsis, disseminated intravascular coagulation (DIC), advanced liver disease, and multi-organ failure frequently alter coagulation profiles in ways that are difficult to predict and monitor[1,3]. In these contexts, early recognition of hemostatic abnormalities and prompt, targeted intervention are crucial to improving patient safety and outcomes.

Conventional coagulation tests (CCTs), while widely available and familiar to clinicians, provide limited insights into the dynamic and multifaceted nature of hemostatic dysfunction. Viscoelastic testing (VET) refers to a group of coagulation testing methods that assess the physical properties of clot formation (CF) in a whole blood sample in real-time[6]. Initially developed for surgical settings, with algorithms validated in liver transplant, cardiac surgery, or trauma, the utility of VET in non-surgical patients who are critically ill is increasingly recognized, offering opportunities for precision-based therapeutic interventions in complex medical conditions associated with coagulopathy[7-9].

CCTs, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), represent the time (in seconds) necessary for soluble fibrin formation after the addition of calcium and an activator of the extrinsic and intrinsic pathways, respectively, in plasma[10]. These CCTs mainly reflect the activity of plasma procoagulant factors, lacking sensitivity for the activity of anticoagulant factors[11]. In addition, the CCTs only consider the plasma components of hemostasis, without accounting for cellular components such as platelets, red blood cells, and leukocytes, thereby failing to reflect the integrated whole-blood environment present *in vivo*. Moreover, laboratory processing requirements can delay results by 30-60 minutes or more, a time that is often critical in patients with bleeding or rapidly deteriorating conditions[12-14].

By contrast, VET – including thromboelastography (TEG) and rotational thromboelastometry (ROTEM) – offers a real-time, global evaluation of coagulation function using whole blood, assessing from the initiation of CF through final lysis [13,15]. This dynamic assessment captures the interplay between plasma coagulation factors, platelets, and fibrinolytic pathways[13,15]. The rapid turnaround time of initial parameters (often within 10-15 minutes) enables immediate, point-of-care decision-making[15]. Additionally, VET can identify both hypocoagulable and hypercoagulable states, detect hyperfibrinolysis, and can help to differentiate surgical from coagulopathic bleeding – capabilities that CCTs largely lack [16,17]. For example, data from modern cohorts demonstrate that CCTs may miss hypercoagulable states in up to 30% of sepsis or liver failure cases, contributing to delays or inappropriate therapy[18-20]. By contrast, VET's dynamic measurements capture the entire clotting process, enabling the detection of hypercoagulability and facilitating faster, evidence-based decisions on transfusion and anticoagulation[19,20]. These advantages translate into more targeted, physiology-based transfusion strategies, minimizing unnecessary blood product administration, reducing transfusion-associated risks, and optimizing resource utilization. VET-guided transfusion algorithms have reduced allogeneic transfusion rates by 20%-40%, shortened time to intervention by 30%-50% compared to CCTs, and improved ICU length of stay in cohort studies[14,21-23].

The use of VET in medical ICUs marks a significant shift from reactive to proactive coagulation management. This narrative critically assesses the role of VET in evaluating and managing hemostasis in the medical ICU. The article provides a brief overview of the fundamental principles of VET technology. It then discusses the key clinical applications of VET in the medical ICU, including the assessment and diagnosis of coagulopathy, and guidance on bleeding management. Finally, the review outlines the limitations and challenges of using VET in the medical ICU, as well as future perspectives for integrating VET into precision-based, individualized hemostatic care for patients who are critically ill.

PRINCIPLES AND TECHNOLOGY OF VET

VET offers a comprehensive, real-time assessment of coagulation from whole blood, including CF, strength, and dissolution[15]. This technology measures the physical properties of blood clotting, providing a more comprehensive picture of hemostasis compared to traditional methods[24]. CF involves the transition of blood from a liquid to a gel, and then a solid state, altering its physical properties. These are assessed either by measuring the movement amplitude of a pin relative to a cup containing the blood, as in traditional TEG and ROTEM assays, or by sonometric methods[25]. The conceptual technology for VET was invented in 1948[12]. The two oldest licensed VET techniques are TEG and ROTEM (with devices known as TEG 5000 and ROTEM Delta, respectively). These tests evaluate the physical properties of the blood clot formed in a cup with a pin suspended inside it[12]. In both technologies, the relative movement of the cup and pin is influenced by the strength of the forming clot[11,15]. Both TEG and ROTEM assess whole-blood hemostasis by measuring the evolving viscoelastic properties of a forming clot. However, the mechanical setup and assay details differ in ways that affect interpretation and clinical utility[15]. In classic TEG, a stationary pin is suspended in an oscillating cup containing citrated whole blood. As the clot forms, fibrin strands transmit torque to the pin, which increases the amplitude of pin deflection and is plotted as a real-time curve quantifying key clotting phases. ROTEM uses a reverse principle: The cup remains static, while the pin rotates; CF impedes pin motion through the sample[15]. The extent of this motion is captured by the VET devices and, with the help of specialized software, is converted into ROTEM or TEG parameters. Table 1 displays the key parameters offered by both viscoelastic devices. An example of a trace with main ROTEM parameters is depicted in Figure 1.

Recent advancements in VET methodologies include the availability of cartridge-based systems (TEG 6S®, ROTEM Sigma). These newer systems offer increased ease of use, greater portability, and more robust results, particularly in out-of-laboratory environments[24]. The ROTEM sigma platform, like its predecessor, the ROTEM Delta, relies on the mechanical transduction of CF *via* a rotating pin and a stationary cup[15,24,26]. However, it is cartridge-based, and a citrated vacutainer can be spiked directly onto the cartridge, distributing the blood into four chambers with rotating pins, eliminating the need for manual pipetting. In some of the newer devices (TEG 6S® and Quantra®), the technology has been updated to utilize resonance-frequency technology and light-emitting diode detection for assessing the physical properties of the clot, rather than the pin-and-cup mechanism[25,27-29].

Modern VET platforms offer multiple specialized assays using different activators and inhibitors to reflect different aspects of hemostasis[15]. For example, ROTEM's EXTEM assay utilizes tissue factor to activate the extrinsic pathway, whereas INTEM employs contact activation for assessing the intrinsic pathway. FIBTEM incorporates platelet inhibition to isolate fibrinogen's contribution to clot strength, and HEPTEM includes heparinase to assess coagulation in patients receiving heparin. TEG and other platforms offer similar assays and key parameters, providing detailed information about hemostasis. This allows clinicians to identify specific defects and guide targeted interventions. However, it is critical to note that results from different platforms and even different models within the same platform (such as TEG 5000 and TEG 6S®) are not interchangeable, even with similar activators, requiring device-specific reference ranges and algorithms [12,24]. Table 2 describes the reagents/activators for the most commonly used TEG and ROTEM assays and their main clinical indications.

CLINICAL APPLICATIONS OF VET IN THE MEDICAL ICU

Coagulopathy assessment and diagnosis

Patients in the medical ICU often develop acquired hemostatic disorders as a result of several underlying conditions, including sepsis, liver dysfunction, DIC, cancer, and the effects of medications[1,5]. VET offers important insights into the specific mechanisms driving coronavirus disease 2019 (COVID-19)-associated coagulopathy, enabling targeted therapeutic interventions.

Sepsis-induced coagulopathy and DIC: Sepsis triggers a complex sequence of hemostatic events, ranging from subclinical abnormalities to overt DIC[30,31]. The pathophysiology involves the activation of coagulation, primarily mediated by tissue factor, the suppression of natural anticoagulant pathways and fibrinolytic mechanisms, as well as endothelial activation and damage[31]. Tissue factor is normally expressed on cells that come in contact with blood after tissue injury to activate clotting and control bleeding. However, in the case of severe infections, microorganisms, pathogen-associated molecular patterns, and damage-associated molecular patterns attach to pattern-recognizing receptors found on immune cells (primarily monocytes and circulating macrophages), prompting the expression of tissue factor on their surfaces, which activates coagulation *via* the extrinsic pathway[31]. Additional factors that contribute to coagulation activation and amplification during sepsis include the enhanced release of extracellular vesicles from various cell types, complement activation, the development of neutrophil extracellular traps, the discharge of polyphosphates from bacteria and platelets, increased platelet activation, and activation of endothelial cells[31,32]. The activated coagulation system, together with the impairment of anticoagulant and fibrinolytic pathways, results in a hypercoagulable state in early sepsis, often associated with microvascular thrombosis and organ dysfunction[32]. Activation of coagulation and interaction with activated platelets and immune cells, resulting in subsequent CF, is known as immunothrombosis – a strategy that contributes to host defense against pathogen spread[33,34]. However, when this process becomes dysregulated, the uncontrolled interaction between the activated coagulation and immune system progresses to DIC. This hypercoagulable state, often observed in the early phases of severe infections, transitions to a hypocoagulable state in more advanced stages, characterized by marked decreases in coagulation factor levels, including fibrinogen, platelet

Table 1 Significance of key parameters used in rotational thromboelastometry and thromboelastography

Parameter on ROTEM	Parameter on TEG	Definition	Significance
CT	Reaction time	Time to 2 mm clot firmness amplitude	Reflects coagulation factor activity and thrombin generation
Clot formation time	Kinetic time	Time from 2 mm to 20 mm clot firmness amplitude	Reflects fibrin polymerization, stabilization of the clot with platelets and factor XIII
α angle	α angle	Angle between the baseline and a tangent to the clotting curve through the 2 mm point	Reflects fibrin polymerization, stabilization of the clot with platelets and factor XIII
MCF	MA	The MA reached during the test	Reflects clot strength depending on platelets, fibrinogen, factor XIII
Lysis index at 30 minutes, 45 minutes, 60 minutes after CT	Lysis index at 30 minutes, 60 minutes after MA (Ly30, 60)	The residual clot firmness at 30 minutes, 45 minutes, 60 minutes after CT (ROTEM) in percentage of MCF. The reduction in clot firmness at 30 minutes, 60 minutes after MA (TEG) in percentage of MA	Reflects clot lysis depending on fibrinolytic activators or inhibitors, factor XIII, and platelet-mediated clot retraction

CT: Clotting time; MA: Maximum amplitude; MCF: Maximum clot firmness; ROTEM: Rotational thromboelastometry; TEG: Thromboelastography.

Table 2 Classic and cartridge-based assays for rotational thromboelastometry and thromboelastography

Assay (platform)	Activator/reagent	Main pathway assessed/information
ROTEM Delta EXTEM	Tissue factor	Extrinsic
ROTEM Delta INTEM	Ellagic acid	Intrinsic
ROTEM Delta FIBTEM	Tissue factor + cytochalasin D (platelet inhibitor)	Fibrinogen, factor XIII
ROTEM Delta HEPTEM	INTEM reagents + heparinase	Intrinsic, heparin effect
ROTEM Sigma Complete cartridge	Includes EXTEM, INTEM, FIBTEM, APTEM	-
ROTEM Sigma Complete + heparin cartridge	Includes EXTEM, INTEM, FIBTEM, HEPTEM	-
TEG 5000 CK	Kaolin	Intrinsic
TEG 5000 CKH	Kaolin + heparinase	Intrinsic, heparin effect
TEG 5000 CRT	Tissue factor (RapidTEG)	Extrinsic
TEG 5000 CFF	Functional fibrinogen (tissue factor + GPIIb/IIIa inhibitor)	Fibrinogen, factor XIII
TEG 6S® Global Hemostasis Cartridge	Includes CK, CK with heparinase, citrated RapidTEG, and citrated functional fibrinogen	-

CK: Citrated kaolin; ROTEM: Rotational thromboelastometry; TEG: Thromboelastography.

counts, and increased hemorrhagic manifestations[30].

VET IN SEPSIS-CURRENT EVIDENCE

Identifying normocoagulability or hypercoagulability in patients with sepsis with altered CCTs

Patients with sepsis often have reduced levels of coagulation factors, leading to prolonged PT and aPTT, suggesting hypocoagulability. However, even if the coagulation factor levels are decreased, they are usually sufficient to support hemostasis. Unlike CCTs, VET can identify hypercoagulability[35]. This is important because it can prevent inappropriate clinical decisions, such as administering pro-coagulant therapies based solely on abnormal conventional test results.

In a large observational study, among patients with sepsis with abnormal CCTs, ROTEM identified 11.8% with hypercoagulation and 20.6% with normal coagulation despite elevated international normalised ratio (INR), and 3.5% hypercoagulable and 24.1% normocoagulable patients among those with thrombocytopenia, showing that CCTs routinely miss hidden hypercoagulability or normocoagulability[20]. Andersen *et al*[36] found that ROTEM analyses reflected an

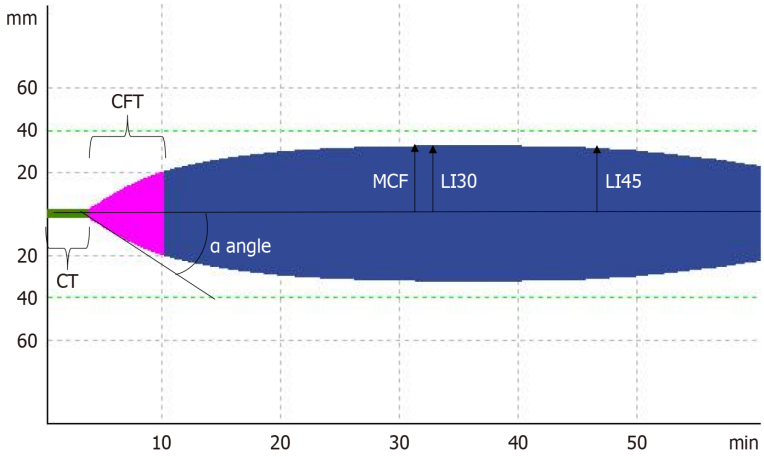

Figure 1 An example of a trace with main rotational thromboelastometry parameters. CFT: Clot formation time; CT: Clotting time; LI30: Lysis index at 30 minutes after clotting time; LI45: Lysis index at 45 minutes after clotting time; MCF: Maximum clot firmness.

overall normocoagulable state in patients with severe sepsis or septic shock, even though their CCTs results were abnormal, revealing prolonged PT, aPTT, and increased fibrinogen levels. Similarly, in another study involving patients in the ICU with sepsis and septic shock, key ROTEM variables largely remained within reference ranges while routine coagulation tests were prolonged[37]. Similar findings were reported by Collins *et al*[38], who demonstrated, using thrombin generation tests, that patients with sepsis generated the same amounts of thrombin as controls, despite having prolonged CCTs. In this study, VET confirmed the findings from thrombin generation tests, with normal or exaggerated CF after a delayed initiation phase (prolonged clotting time [CT] while the alpha angle and clot firmness were increased) in patients with sepsis[38]. Other research has also shown a hypercoagulable state in sepsis compared to healthy controls, as revealed by shorter CTs and CF times (CFTs), increased alpha angle, maximum clot firmness (MCF) or amplitude, despite abnormal CCTs[39,40]. Davies *et al*[41] found mildly prolonged CTs in patients with septic shock, with CTs increasing with sepsis severity; however, other ROTEM parameters, such as the CFT, alpha angle, and clot firm-ness remained within the normal range or were increased compared to the healthy control, indicating normocoagula-bility or hypercoagulability.

The initial phases of sepsis generally demonstrate a hypercoagulable state, which progresses to a hypocoagulable condition in the later stages. However, these alterations in the coagulation system remain undetectable by CCTs, which are prolonged in sepsis from the early phases, suggesting hypocoagulability. The prolongation of CCTs reflects the deficiency of procoagulant factors; however, in sepsis, both anticoagulant and procoagulant factors, with the exceptions of factor VIII and fibrinogen, are decreased. Similar to CCTs, VET may not be sensitive enough to reflect the correct balance between procoagulant and anticoagulant factors, and might underestimate hypercoagulability in patients with sepsis[11]. In general, with VET, activated assays are less sensitive to the deficit of anticoagulant factors compared to non-activated assays[42]. Another aspect is that, although VET is performed using whole blood, it does not include the endothelial cells, which play a significant role in activating the natural anticoagulant pathways.

Whole-blood VET takes into account the role of cellular components in blood coagulation, and from this point of view, performs better than CCTs. However, since endothelial cells are absent in these tests, the natural anticoagulant pathways are not activated, leading to an incomplete representation of these pathways in VET analysis. Consequently, tests that do not permit complete activation of protein C, including VET, do not accurately represent the equilibrium between procoagulant and anticoagulant factors[11].

Diagnosis of low fibrinolysis (fibrinolysis resistance or shutdown)

Fibrinolysis, the process of breaking down clots, is essential for restoring blood flow in the vascular system. In sepsis, the impairment of fibrinolysis primarily caused by the overproduction of plasminogen activator inhibitor-1 is a significant concern, as it is associated with microcirculatory dysfunction, increased disease severity, and worse patient outcomes[11,43]. CCTs do not help estimate fibrinolytic activity. The specialized laboratory tests for fibrinolysis are cumbersome, time-consuming, and are usually not performed around the clock in most clinical laboratories[44]. Point-of-care tests based on viscoelastic technology are widely available and frequently used for fibrinolysis assessment[11]. The most commonly used viscoelastic platforms in clinical practice, TEG and ROTEM, estimate the fibrinolytic activity based on the decrease in clot firmness compared to the maximum value obtained during measurement[45]. Patients with sepsis[46-48] usually maintain their clot firmness, demonstrating significantly lower clot lysis compared to healthy controls or patients without sepsis[49-52].

However, differentiating low fibrinolytic activity from normal results using VET is more challenging than detecting hyperfibrinolysis by increased clot lysis visible during measurement, which usually leads to abnormal values of clot lysis indices and/or maximum lysis (ML). The challenge stems from the fact that healthy individuals usually display minimal clot lysis at baseline, and the changes in clot amplitude measured are often subtle. In a study conducted by Lang *et al*[53] that analyzed ROTEM data from healthy individuals at various centers, the clot lysis index and ML values included 0% lysis. Consequently, alternative methods were developed to enhance the sensitivity of low fibrinolytic activity as mea-

sured by VET. A recent publication presented a new early kinetic parameter, known as time to attain maximal clot amplitude after reaching maximal CF velocity, representing the time required to reach maximal clot amplitude after achieving the highest CF velocity[46]. The values of this calculated parameter were higher in sepsis than in healthy controls and correlated with lower fibrinolytic activity[46]. In six studies, adjustments to VET by including fibrinolysis activators in the assays have been used to improve the evaluation of fibrinolysis[46,47,54-57]. Patients with sepsis showed impaired clot lysis in response to fibrinolytic activators, revealing fibrinolysis resistance, which may be missed with standard VET[46,47,54-57].

Identifying patients with overt DIC

Sepsis is the most common underlying cause of DIC, which occurs in approximately 30%-50% of sepsis cases[58]. The diagnosis of DIC is based on various scoring systems, the most widely used being the International Society on Thrombosis and Haemostasis overt DIC score, published in 2001 and revised in 2025, and the Japanese Association for Acute Medicine DIC score[59-61].

DIC is a dynamic entity, progressing from an early, non-overt phase to overt DIC, which is often complicated by clinical manifestations such as bleeding or organ dysfunction, and increased mortality[59,60]. In most cases, the diagnosis of early (non-overt) DIC is missed, being detected only in the phase of overt DIC, when patients develop clinical symptoms of hemorrhage or thrombosis. Nevertheless, during the early phase of non-overt DIC, VET can indicate the activation of coagulation and hypercoagulability, which standard coagulation tests fail to identify[11]. VET can easily identify a hypercoagulable state by shortened CTs, increased clot strength, and decreased clot lysis. In a study conducted by Schöchl *et al*[62], the activation of coagulation induced by intravenous endotoxin administration in animals was detected using ROTEM. By contrast, CCTs failed to detect this activation.

As sepsis advances, the VET parameters change, revealing longer reaction time and CTs, reduced clot strength (maximum amplitude [MA]/MCF), and heightened clot lysis. These changes signal depletion of clotting factors, consumption of platelets, and disturbances in fibrinolysis, which are characteristic features of overt DIC[49,63-66]. According to the updated DIC definition from 2025, DIC is a dynamic condition, and VET testing enables the ongoing evaluation of coagulation status, documenting the specific hemostatic alterations at each stage. Furthermore, diagnosing DIC using a scoring system usually involves a comprehensive assessment of various laboratory indicators, including PT prolongation, platelet count, fibrinogen concentration, and fibrin degradation products. These measurements often require time, leading to unwanted delays in DIC diagnosis, and cannot differentiate between prothrombotic and bleeding states. By contrast, VET offers a more rapid and comprehensive assessment of the hemostatic status[66].

Outcome prediction

Outcome prediction in patients with sepsis using VET represents a significant and emerging frontier in personalized critical care. The prognostic utility of VET in sepsis is linked to its ability to detect specific coagulation patterns. Studies have shown that an initial hypercoagulable state, particularly in the early stages of sepsis, is correlated with a significantly higher mortality rate compared to patients without coagulation changes[38,67]. CCTs and even severity scores often fail to detect this group of patients with hypercoagulation with an increased mortality risk[67]. In sepsis, the transition to hypocoagulability (characterized by prolonged CTs and reduced clot strength) signals progression towards DIC, bleeding complications, and high mortality[63,68]. The improvement in coagulation parameters, such as a decrease in prolonged CT and correction of low clot strength during ICU stay, was correlated with improved organ dysfunction and outcomes at ICU discharge[37,57].

Impaired fibrinolysis measured using VET in patients with sepsis was associated with increased risk of thrombotic complications and short-term mortality, even after adjusting for clinical severity scores in six studies[41,47,48,51,57,65]. Prakash *et al*[69] showed fibrinolysis impairment correlated with increasing severity of organ failure in sepsis, both at presentation and prospectively. Furthermore, patients who demonstrated an increase in fibrinolytic activity also showed an improvement in sepsis-related organ failure and better outcomes[69]. These findings suggest that VET-derived fibrinolysis markers may provide incremental prognostic information beyond standard clinical indices, although their routine use is limited by standardization and availability concerns.

VET IN CRITICALLY ILL PATIENTS WITH COVID

COVID-19-associated coagulopathy (CAC) is a significant and frequently observed complication in patients with COVID-19, often correlated with severe disease and increased mortality[70]. While it shares fundamental similarities with DIC, such as systemic activation of coagulation stemming from microvascular damage, CAC is specifically characterized as a thrombotic phenotype of DIC due to its unique clinical and laboratory features[70]. A defining characteristic of CAC is the high incidence of thrombotic events, including macrothrombosis (deep vein thrombosis, pulmonary embolism, thrombotic stroke, and acute coronary syndromes) and microvascular thrombosis within the lungs and other organs.

These thrombotic complications are notably more frequent in CAC compared to sepsis-induced coagulopathy/DIC. Typical laboratory findings in CAC include markedly elevated D-dimer levels (often greater than twice, and sometimes five times, the upper limit of normal) and increased fibrinogen levels (hyperfibrinogenemia)[70-72]. These findings contrast with the usual decrease in platelet count and prolongation of PT often observed in sepsis. In cases of CAC, platelet counts are typically preserved initially, showing only mild reductions in severe instances. Additionally, the coagulation tests (PT and aPTT) usually remain normal or are only slightly prolonged[73]. This distinct pattern, known as "thromboinflammation", indicates in most severe COVID-19 cases a hypercoagulable phenotype instead of a con-

sumptive one[74]. While bleeding events are uncommon in the early phase of CAC, they may arise as the disease advances[70].

CCTs such as PT, aPTT, and platelet counts do not fully capture the complexity of CAC[75]. In this context, VET has become an essential tool for providing a more comprehensive and dynamic evaluation of global hemostasis in critically ill COVID-19 patients. Research utilizing ROTEM and TEG in critically ill patients with COVID-19 consistently demonstrates a condition of hypercoagulability, revealed by enhanced clot strength (MCF or MA), accelerated CF (shorter CFT), and/or shortened CTs (CT in ROTEM, reaction time in TEG) compared to controls[73,76-79]. This hypercoagulable state is often present early after hospital admission, even in patients with mild to moderate disease, and becomes more pronounced with increasing disease severity[73]. In some studies, clot firmness and the contributions of both platelets and fibrinogen to clot strength were elevated[80,81]. The ability to generate thrombin in patients with COVID-19 has been noted to stay at normal levels or even rise, despite prophylactic anticoagulation, indicating a notable baseline hypercoagulability that standard heparin treatment may not completely control[82,83].

Many critically ill patients with COVID-19 exhibit a decreased fibrinolytic capacity or "fibrinolysis shutdown", meaning the clots formed are resistant to breakdown, which increases susceptibility to both macrovascular and microvascular thrombosis; this is often observed as low lysis on TEG or on ROTEM (indicating absence of enhanced fibrinolytic activity)[73,78,82]. CCTs cannot detect this phenotype, and thromboembolic complications can occur despite standard prophylactic anticoagulation[81,84]. This state, characterized by low fibrinolytic activity, can paradoxically coexist with high D-dimer levels. This contradiction may be attributed to localized fibrinolysis in the lungs generating D-dimers while systemic fibrinolysis remains inhibited. Increased levels of plasminogen activator inhibitor-1 are strongly associated with decreased fibrinolytic activation[78,82,85]. Wright *et al*[78] demonstrated that high MA and low clot lysis at 30 minutes by TEG independently predicted thrombotic complications in patients in the ICU with COVID-19. Patients with fibrinolysis shutdown had worse clinical outcomes, supporting the potential utility of VET in guiding intensified thromboprophylactic or even thrombolytic interventions.

While most patients with COVID-19 in the ICU are hypercoagulable, some may develop bleeding diatheses due to advanced disease, superimposed sepsis, or escalated anticoagulation regimens[72,86]. The dynamic, point-of-care nature of VET makes it a valuable bedside tool for balancing the risk of thrombosis and bleeding, especially when considering dose modulation of heparins or alternative anticoagulants. VET can identify hypocoagulable states that may prompt de-escalation or reversal of anticoagulation[72,87].

Despite their utility, the application of VET in COVID-19 has limitations, for several reasons: (1) Many studies on this topic are retrospective or involve small sample sizes, limiting the generalizability and predictive power of their findings; (2) There is variability in testing patterns and the timing of sample collection relative to disease progression or anticoagulant administration; and (3) Standardized protocols for ROTEM/TEG in COVID-19, particularly for assessing thrombin generation in the presence of heparins and high fibrinogen, or the modified VET tests for assessing fibrinolytic activity, are still being developed and validated. Further prospective, randomized controlled trials (RCTs) are warranted to establish the predictive role of VET for clinical outcomes and to guide personalized antithrombotic treatment strategies in patients with COVID-19.

VET IN THE ASSESSMENT OF THE COAGULOPATHY OF CHRONIC LIVER DISEASE

Patients with cirrhosis exhibit a complex and frequently opposing set of changes in their hemostatic system, commonly referred to as "rebalanced hemostasis". This condition features concurrent modifications that promote both hemorrhage and clotting, which generally counterbalance one another[88-90]. For instance, reduced plasma levels of coagulation factors, inhibitors of coagulation, and fibrinolytic factors are observed due to defective hepatic synthetic capacity. At the same time, the number of circulating platelets decreases due to several factors, including reduced synthesis of thrombopoietin, splenomegaly, and increased platelet turnover[18,88]. However, these changes are often counterbalanced by higher plasma levels of hemostatic proteins, such as von Willebrand factor, that are produced by endothelial cells[88,91,92]. The longstanding perspective of cirrhosis being a bleeding disorder has been questioned, as CCTs (*e.g.*, PT, aPTT, and platelet count) often fail to capture this complex rebalanced state and do not reliably predict bleeding risk[90]. This rebalanced state, however, is fragile and can easily be tipped towards either hypocoagulable (bleeding) or hypercoagulable (thrombotic) conditions, especially in the presence of acute clinical insults[90].

Patients who are critically ill with cirrhosis represent a particularly vulnerable population facing complex hemostatic challenges. The specific coagulation changes observed in patients in the ICU with different stages of cirrhosis, and their assessment by CCTs and VET, are described below.

Compensated cirrhosis

Patients with compensated cirrhosis, despite showing abnormalities in CCTs (*e.g.*, prolonged international normalized ratio and thrombocytopenia), typically maintain a normal or even increased capacity for thrombin generation when assessed using global hemostasis assays, particularly in the presence of thrombomodulin[93,94]. This is due to a parallel reduction in both plasmatic procoagulant and anticoagulant factors[90,93]. Some studies indicate that compensated cirrhosis, particularly Child-Pugh A, is associated with an increased thrombin generation capacity (hypercoagulability), which can be attributed to factors like elevated Factor VIII and decreased protein C[18,91,92,95]. In stable compensated cirrhosis, TEG parameters are often within normal limits[19]. Patients with cholestatic liver diseases (*e.g.*, primary biliary cirrhosis, primary sclerosing cholangitis) may even demonstrate relative hypercoagulability by TEG compared to those with non-cholestatic liver diseases or healthy individuals[19,96]. Similarly, ROTEM analysis in stable cirrhosis generally

shows parameters within normal ranges despite altered CCTs[97].

Acute decompensation

In decompensated cirrhosis, the rebalanced hemostatic system becomes more vulnerable to imbalance, and patients may exhibit both hypocoagulable and hypercoagulable features[98-100]. Although still largely used, traditional coagulation tests such as PT and INR are often misleading when assessing bleeding risk in patients with decompensated conditions [88]. In a subset of patients with decompensated cirrhosis and INR ≥ 1.5, TEG studies showed that the mean clot MA was below normal limits, likely due to lower platelet counts, and the alpha-angle was depressed in those with hypofibrinogenemia[19]. The VET parameters in patients with acute decompensation reflect hypocoagulability less often compared to patients with acute-on-chronic liver failure (ACLF). They are often relatively stable or even improving, as evidenced by ROTEM values in the short term, contrasting with the worsening seen in ACLF[101,102]. A prospective study demonstrated that TEG parameters associated with hypocoagulability (prolonged k-time, reduced α-angle, and reduced MA) could predict procedure-related bleeding in decompensated cirrhosis[100]. Some studies using VET did not find a correlation between parameters reflecting hypocoagulability and higher bleeding risk in decompensated cirrhosis[101-104]. This is likely because bleeding events in patients with cirrhosis often stem from portal hypertension rather than coagulopathy. However, other concomitant factors such as acute kidney injury (AKI) and bacterial infection significantly increase the risk for procedural bleeding in decompensated cirrhosis[92,99,100]. Sepsis, in particular, has been linked to increased circulating endogenous heparinoids, which can contribute to a higher bleeding risk[19,105]. Low fibrinogen levels can also be associated with spontaneous and procedure-related bleeding, potentially reflecting critical illness[88, 105].

ACLF

ACLF is defined by acute hepatic decompensation accompanied by the failure of at least one major organ system, including coagulation, and carries a high short-term mortality[106]. There is considerable individual variability in global hemostatic profiles of patients with ACLF[105]. Patients who are critically ill with ACLF can present both hypocoagulable and hypercoagulable features. Recent studies using whole blood thrombin generation indicate a significant hypocoagulable state in decompensated cirrhosis, especially in Child-Pugh C patients with ACLF, contradicting earlier findings from platelet-poor plasma thrombin generation that suggested hypercoagulability[107]. This hypocoagulable state is exacerbated by bacterial infections and the severity of anemia[107].

ROTEM measurements in patients with ACLF show worsening hypocoagulability shortly after admission, characterized by delayed CF and decreased clot firmness[101]. This derangement correlates with the severity of liver disease and bacterial infection and is associated with poorer outcomes[101]. Similarly, abnormal TEG parameters, such as a prolonged R-time, K-time (> 9 minutes), and low MA (< 18 mm), have been described in ACLF[108]. Thrombocytopenia and hypofibrinogenemia are frequent in ACLF and are associated with the hypocoagulable state observed in patients with ACLF with bleeding[109].

Despite the hypocoagulable tendencies, patients with ACLF still exhibit prothrombotic elements. Elevated von Willebrand factor levels and decreased ADAMTS13 levels are particularly pronounced in ACLF and are independently associated with 30-day mortality, correlating with organ failure and disease severity[92,102]. Patients with ACLF display mixed fibrinolytic phenotypes, ranging from hypofibrinolysis to hyperfibrinolysis, with hypofibrinolysis being noted in those with complications and poor survival[88,92,102]. However, fibrinolytic potential does not consistently predict bleeding in ACLF[102].

Bleeding management guided by VET

Bleeding in patients who are critically ill is usually due to various causes involving imbalances in different hemostatic pathways. The current understanding of hemostasis utilizes the cell-based coagulation model, which highlights that coagulation occurs on the surfaces of cells through four sequential phases: (1) Initiation; (2) Amplification; (3) Propagation; and (4) Stabilization. This model emphasizes the critical role of platelets, endothelial cells, and the interaction between cellular and plasma components in maintaining hemostatic balance[110]. The biochemical environment, including pH, temperature, and calcium levels, has a critical influence on thrombin generation and CF, making the optimization of these parameters essential for adequate hemostasis[111].

To facilitate bedside interpretation and optimize therapeutic decision-making, coagulation can be functionally classified into three phases based on VET parameters: (1) Thrombin generation phase: Determined by enzymatic coagulation factors and influenced by the biochemical environment, anticoagulants, inhibitors, and factor deficiencies. This phase is represented by CT in ROTEM and reaction time in TEG; (2) Clot firmness phase: Determined by fibrin polymerization, platelet aggregation, platelet-fibrin interactions, and factor XIII activity. This phase corresponds to amplitude measurements at specific time points and MCF in ROTEM, or MA in TEG; and (3) Clot stabilization phase: Determined by fibrinolysis, factor XIII activity, and platelet-mediated clot retraction. This phase is represented by lysis parameters, including ML and lysis indices at various time points[112].

VET enables targeted, precision-based therapeutic interventions by identifying specific hemostatic defects. Rather than empirical administration of multiple blood products, VET results can guide selective use of platelet concentrates, fresh frozen plasma, factor concentrates, or antifibrinolytic agents based on the specific defect identified[113]. This targeted approach has been associated with reduced transfusion requirements, decreased costs, and potentially improved patient outcomes[8,23]. In complex cases where challenging decisions about hemostatic therapies need to be made, VET allows for "virtual" treatment trials. In this process, patient samples are combined *in vitro* with different therapeutic agents, and re-testing is performed, enabling real-time predictions of treatment responses before actual administration. This feature has the potential to improve therapeutic precision and minimize unnecessary interventions.

One of the most valuable applications of VET in clinical practice is the hemostasis assessment and VET-guided periprocedural management of patients with complex coagulopathies and altered CCTs before various invasive procedures. Often, patients with sepsis or cirrhotic coagulopathy and prolonged CCTs have VET results suggesting normocoagulability or hypercoagulability; therefore, the invasive procedures can be performed without any prophylactic correction of hemostasis[64]. This strategy prevents overcorrection of the coagulation system, thereby reducing hypercoagulability, and generally decreases the need for blood product transfusions or procoagulant therapies in patients who are critically ill. The most compelling evidence for the usefulness of VET in critically ill patients with cirrhosis comes from RCTs evaluating its role in guiding blood product transfusion not only in surgical settings, but also in patients who are critically ill with variceal or non-variceal bleeding, or undergoing invasive procedures[21,22]. Two systematic reviews and meta-analyses found that VET-guided therapy significantly reduced blood product use in patients with cirrhosis compared to standard practice[21,22]. Similarly, more research in adult and pediatric patients with cirrhosis and abnormal CCTs scheduled for invasive procedures has shown lower blood product requirements when a VET-guided hemostatic management strategy is applied compared to the standard of care based on CCTs[114,115].

LIMITATIONS AND CHALLENGES

Recent studies on VET in the medical ICU are marked by substantial heterogeneity in patient populations, clinical indications, and diagnostic endpoints. This diversity often complicates the direct comparison of results and limits the generalizability of findings across healthcare settings. Most published evidence arises from single-center observational studies or small RCTs, with variable methodological quality and frequent risk of bias in patient selection, outcome reporting, and intervention protocols. Although the advantages of VET in critical care environments are becoming increasingly acknowledged, notable constraints and challenges still impede its broader adoption in medical ICUs. These obstacles cover technical, educational, and financial aspects.

Technical limitations

VET assesses hemostasis using whole blood samples, showing the contribution of both plasmatic and cellular components of hemostasis, as opposed to CCTs, which are performed from plasma. However, VET also has limitations that must be considered in clinical decision-making. The tests are performed under static conditions without the contribution of endothelial cells or vessel wall to hemostasis, as *in vivo* conditions[116]. Additionally, similar to CCTs, VET is typically performed at 37 degrees Celsius, which may not always be the patient's body temperature. However, the temperature can be modified in most VET platforms.

VET is poor at detecting conditions that affect platelet adhesion, such as von Willebrand's disease. The tests are also insensitive to aspirin, P2Y12 inhibitors, or LMWH, which limits their ability to assess the full spectrum of hemostatic function[117]. The standard VET assays, including TEG and ROTEM, lack sensitivity for detecting drug-induced platelet dysfunction, leading to under recognition of residual platelet inhibition and the potential for inappropriate therapeutic decisions in high-risk cases[117]. Another issue is related to pre-analytic factors and sample handling requirements, which can affect the accuracy of results if not adequately controlled.

Unlike automated central laboratory platforms, VET devices are typically operated by clinical staff rather than laboratory technicians, creating unique quality control challenges. Regular external quality assessments and proficiency testing are recommended to maintain consistency and reliability, but implementing these standards in busy ICU environments proves challenging.

Training and education

Successful implementation of VET-guided bleeding management requires comprehensive training programs for clinical staff. VET interpretation requires structured educational initiatives that cover both the technical aspects of testing and clinical decision-making algorithms[8,117]. Additionally, different VET platforms employ varying algorithms and therapeutic targets, which can lead to confusion when transitioning between systems. The lack of standardized therapeutic targets across different clinical scenarios remains a significant challenge.

Economic and resource constraints

The initial capital investment required for VET implementation can be substantial, particularly for smaller hospitals or resource-limited settings. Ongoing reagent costs and staff training requirements add to the economic burden, though these are typically offset by long-term savings from reduced transfusion requirements[118,119]. Smaller medical ICUs may face challenges in justifying the implementation costs of VET, while larger centers with high volumes of patients with coagulopathy are more likely to achieve economic benefits. Careful consideration of institutional factors is necessary before VET implementation. Geographic variations in device availability and technical support can limit access to VET technology in certain regions. Reimbursement policies for VET testing vary significantly between healthcare systems, potentially creating financial barriers to implementation.

Additionally, economic analyses remain scarce, with few evaluations quantifying the cost-effectiveness or budget impact of VET-guided approaches in medical ICUs. Real-world implementation is further challenged by institutional differences in resource availability, training, and digital integration of VET data into clinical workflows. Future research should prioritize well-designed implementation studies, focusing on operational feasibility, user training, adherence to diagnostic algorithms, and cost-benefit analyses to support the sustainable adoption of this practice in routine ICU settings.

CONCLUSION

Even with extensive research in cardiac surgery and trauma environments, there is still insufficient high-quality data on the utilization of point-of-care methods for patients who are critically ill. The existing evidence supporting VET in patients in the medical ICU remains limited compared to surgical populations, leading to ambiguities regarding the best implementation strategies and the potential clinical advantages. Despite these challenges, the potential benefits of VET in medical ICUs warrant continued development and implementation efforts. The benefits of using VETs in the management of major hemorrhage, namely faster identification of coagulopathies and reduced transfusion requirements, have been observed in the general ICU.

To address current limitations, institutions should independently assess the feasibility of establishing a viscoelastic point-of-care service, considering its applicability to their patient cohort, the associated financial costs, and the personnel required. Achieving success requires thorough planning that addresses technical, operational, educational, and economic challenges through systematic approaches to implementation and continuous quality oversight. The evolution of VET technology toward more automated, user-friendly systems may help address some current limitations, but fundamental challenges related to standardization, training, cost, and clinical validation will require continued attention from the medical community, industry, and regulatory bodies.

The integration of artificial intelligence promises to transform VET from a diagnostic tool into an intelligent clinical decision-support system. Future AI applications may include automated pattern recognition for coagulopathic states, predictive modeling for assessing bleeding risk, and real-time treatment recommendations. These systems could analyze complex combinations of VET parameters alongside patient clinical data to provide personalized treatment algorithms that adapt to individual patient characteristics and clinical contexts.

The future of VET in medical ICUs promises dramatic improvements in hemostatic monitoring and management through technological innovation, artificial intelligence integration, and personalized medicine approaches. Success will depend on the collaboration of clinicians, researchers, industry partners, and healthcare administrators to overcome current challenges and use the full potential of these advancing technologies. The ultimate goal remains improved patient outcomes through more precise, timely, and effective hemostatic management in critical care settings.

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